

HUMAN LEPTOSPIROSIS - A REVIEW**Sharon Sunil*, Janet Jacob and Bincy Varghese**

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Correspondence for*Author****Sharon Sunil**Department of Pharmacy
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Bangalore, India.**ABSTRACT**

Leptospirosis is one of the most recognized zoonotic diseases around the world. It is a zoonotic disease caused by spirochetes belonging to genus *Leptospira* which affects both animals and humans. Leptospirosis has been recognized as an important emerging zoonotic disease because of its epidemic presence and increasing incidence in both developing and developed countries. Leptospirosis is still a major public health problem in tropical countries, with epidemic outbreaks occurring in the rainy season and after floods. *Leptospira* are transmitted in the urine of infected carrier animals. Rats are universal reservoirs for this spirochetal zoonosis, although farm animals and livestock can also acquire the infection. Infection occurs when

spirochetes in contaminated water or soil enter microabrasions on the skin or intact mucous membranes. The infection may be nonsymptomatic or may result in different clinical conditions ranging from fever, malaise, myalgia, meningism, and conjunctivitis, as well as anorexia, abdominal pain, nausea, and vomiting. Initial signs of serious infection can include jaundice, hemorrhage, and hepatosplenomegaly. The most severe form of leptospirosis is called Weil syndrome which can result in hepatic and renal failure or massive pulmonary hemorrhage; both forms can progress rapidly to death if untreated. The present review highlights the leptospirosis, epidemiology, susceptible population, disease transmission, clinical manifestation, pathogenesis, diagnosis and management along with effective preventive strategies with a view to combat this organism having public health significance.

KEYWORDS: Leptospirosis, Weil's disease, *Leptospira*.**INTRODUCTION**

Leptospirosis is a zoonotic disease with a worldwide distribution caused by spirochetes belonging to genus *Leptospira*. Leptospirosis is now recognised as an emerging infectious

disease. Leptospirosis, commonly known as “rat-urine fever” in certain countries is transmitted directly or indirectly from animals to humans.^[1-2] The disease is found mainly when human come into contact with carrier animals or environment contaminated with Leptospire. Although rats and other rodents are the primary hosts, a wide range of other mammals including dogs, cattle, sheep, and pigs also carry and transmit the disease as secondary hosts.^[3-5] Humans get infected through skin contact with water or soil containing urine from infected animals or by consuming contaminated food or water. Human-to-human transmission is rare to occur.^[3, 5, 6, 7] Leptospirosis is usually a biphasic illness where the first phase is called the acute or septicaemia phase and the second phase as immune phase.^[4, 8] Over the last decade, outbreaks during sporting events, adventure tourism and disasters underscore the ability of the disease to become a public health problem in nontraditional settings. Yet leptospirosis is mostly a neglected disease which imparts its greatest burden on impoverished populations from developing countries and tropical regions.^[9-11] Leptospirosis, in addition to being an endemic disease of subsistence farmers, has emerged as a widespread problem in urban slum populations where inadequate sanitation has produced the conditions for ratborne transmission of the disease. Leptospirosis is known to be endemic in India since the early 20th century.^[12-14]

EPIDEMIOLOGY

Leptospirosis is an infectious disease of worldwide distribution. Human infection can occur either through direct contact with infected animals or, much more commonly through indirect contact with water or soil contaminated by urine of infected rodents or animals. Person-to-person transmission is extremely rare. Most human infections occur in young adult men and children and result from occupational or environmental exposure.^[15] Epidemiological studies indicate that infection is commonly associated with certain occupational workers such as farmer, sewage worker, veterinarian, and animal handler. Leptospirosis can also be transmitted during recreational activities such as hiking, picnicking, swimming and canoeing.^[16-18] The disease is endemic in tropical areas, areas with heavy precipitation, and areas with high levels of subsurface water. Hence, China, Southeast Asia, Africa, and South and Central America have immense areas where the disease is endemic. Large epidemics are reported after monsoons and periods of unusually heavy rainfall. In India, Kerala, Tamil Nadu and Andamans are endemic for leptospirosis. But now with better facilities to detect the disease, the disease is being reported from almost all parts of India.^[19-24]

MODE OF TRANSMISSION

Human leptospiral infections may be due to the direct or indirect exposure to urine of infected animals. Moisture is an important factor of the survival of the leptospires in the environment. Other modes of transmission of infection include handling infected animal tissues and ingestion of contaminated food and water. Leptospires can gain entry into humans through cuts and abrasions in the skin, through intact mucous membranes (nose, mouth, eyes) and also through waterlogged skin. They may occasionally enter the human body via the inhalation of droplets of urine or through drinking-water.^[25]

CLINICAL MANIFESTATION

Leptospirosis in humans is characterized by a wide variety of symptoms and a biphasic course of illness.^[26] The first phase corresponds to the multiplication and spread of the organism throughout the body. The second phase is characterized by the development of circulating antibodies and the detection of leptospires in the urine. The incubation period is typically 1 to 2 weeks. Most infections appear to be subclinical or so mild that they are never reported. Among clinical cases, initial influenza-like signs during the first phase include fever, headache, chills, myalgias, and, occasionally, a maculopapular skin rash and conjunctival suffusion (i.e., redness of the conjunctiva without inflammatory exudates). This phase is followed by a 1- to 3-day period of symptomatic improvement. In the second phase, the signs of leptospirosis are more organ specific,^[27] and the disease can be categorized into anicteric and icteric forms. The milder anicteric form of the disease is diagnosed in approximately 90% of patients, whereas the severe, icteric form is diagnosed in 5% to 10% of patients. In persons with anicteric leptospirosis, aseptic meningitis is the most common clinical syndrome and is characterized by severe headache and neck stiffness; this syndrome is more common in younger patients.^[28] Uveitis may develop during this phase or may develop weeks to years after the onset of disease. The more severe form, icteric leptospirosis (also called Weil's syndrome), has a less pronounced biphasic course. After initial nonspecific signs, the second phase is characterized by jaundice, renal dysfunction, pulmonary dysfunction, or hemorrhagic manifestations. Untreated patients with the icteric form have a higher mortality rate than those with the anicteric form of leptospirosis. The most severe complication of icteric disease is the development of oliguria; subsequently, anuria and renal failure develop, the latter being the most common cause of death.^[29]

PATHOGENESIS

Pathogenesis of Leptospire is that they enter the body through abrasions macerated skin or cuts, conjunctiva, or by inhalation of aerosols or of water in near-drowning or swimming immersions. The bacteria spread through the bloodstream and tissues without initial inflammatory localization. They grow in any or all tissues until their numbers are large enough to cause local or general lesions. Once antibody appears, after a period of 7-10 days, leptospire disappear from the bloodstream and tissues, except for privileged sites such as the anterior chamber of the eye, and the brain.^[30]

DIAGNOSIS

Specific Diagnosis

Isolation of organism

1. before tenth day of illness

Blood

- i. Dark field examination of the patient's blood
- ii. Culture on a semisolid medium (eg. Fletcher's EMJH)

2. After tenth day of illness:

Urine

- i. Dark field examination of the patient's urine
- ii. Culture of urine (for several months in untreated patient)

Serology

Agglutination tests: Paired sera (fourfold or greater rise in titer)

- i. Microscopic, using live organisms (MAT)
- ii. Macroscopic, using killed antigen

ELISA IgM and Slide agglutination tests (SAT)

- Measure IgM antibodies
- Single sample adequate
- The ELISA IgM test helpful for early diagnosis (positive 2 days into illness)

Dot-ELISA and dip-stick methods

- Newer screening methods (for detecting IgM antibodies)

PCR test Leptospiral DNA

- Detected in blood, urine, CSF, and aqueous humor

Definitive diagnosis of leptospirosis depends on:

- (i) Isolation of organism
- (ii) Serological tests
- (iii) Detection of specific DNA ^[31, 32]

ISOLATION OF ORGANISM

(i) Blood: The organism may be identified by dark field examination of the patient's blood or by culture on a semisolid medium (eg. Fletcher's EMJH i.e. Ellinghausen-McCullough-Johnson-Harris), if taken before the tenth day of illness. Cultures take 1-6 weeks to become positive.

(ii) Urine: The organism may be isolated from the urine on dark ground microscopy tenth day onwards, and in untreated patient, may be recovered on urine culture for several months.

SEROLOGY

Diagnosis is usually made by means of serologic tests, of which several are available.

- (i) Agglutination tests (microscopic, using live organisms; and macroscopic, using killed antigen) become positive after 7-10 days of illness, peak at 3-4 weeks, and may persist at high levels for many years. Thus, to make a diagnosis, a fourfold or greater rise in titer must be documented. The agglutination tests are cumbersome to perform and require trained personnel.
- (ii) ELISA IgM and slide agglutination tests (SAT) are also available.

As ELISA IgM and Slide agglutination tests (SAT) are simple, sensitive tests which measure IgM antibodies, they are used to diagnose current leptospirosis at a very early stage and a single sample is adequate. The IgM ELISA test is particularly useful in making an early diagnosis, as it is positive as early as 2 days into illness, a time when the clinical manifestation may be nonspecific. It was found to be 100% sensitive and 93% specific in one study.^[20] Dot-ELISA and dip-stick methods for detecting IgM antibodies are newer screening methods.

PCR test: PCR methods appear to be sensitive, specific, positive early in disease, and able to detect leptospiral DNA in blood, urine, cerebrospinal fluid (CSF) and aqueous humor.

Currently major disadvantage with these tests is that these are genus specific, not serovar specific.

SPECIFIC SEROVAR

The investigation of choice to identify specific serovar is microscopic agglutination test (MAT) and culture isolation. However, culture growth may take several weeks. Microscopic agglutination test (MAT) is the Gold Standard test, but it is complicated and less sensitive compared to newer tests like ELISA IgM and SAT. ELISA IgM and Slide agglutination tests (SAT) are simple, sensitive tests and can be used to diagnose current leptospirosis.^[33]

MANAGEMENT

Leptospirosis presents with an extensive spectrum of clinical manifestations^[34]. Disease presents in 2 phases: an acute/initial phase followed 5 to 7 days later by the immune phase. Approximately 90% of affected patients will have a self-limited, subclinical illness with an uneventful recovery. The remaining patients may present with severe illness associated with the immune phase presenting with multi-organ failure that can result in death. Management of renal failure, hepatic failure, pulmonary haemorrhages and myocarditis need to be considered along with antibiotic treatment. Other presentations during this phase include aseptic meningitis and pancreatitis. Death may occur secondary to cardiac arrhythmias, cardiac failure, or adrenal hemorrhage.

Effective management of leptospirosis involves a combination of antibiotic therapy and aggressive supportive therapy for patients with organ damage.

ANTIBIOTIC THERAPY

It is generally accepted that antibiotic therapy must be initiated as soon as possible, preferably during the first 5 days of the appearance of symptoms.^[35]

Antibiotic recommendations for the management of leptospirosis are provided according to disease presentation. Preferred antibiotic agents include oral doxycycline for mild disease and intravenous benzylpenicillin for the management of severe cases.^[36, 37]

Patients must be carefully monitored for adverse reactions including the Jarisch-Herxheimer reaction, which can be fatal.^[38]

MILD DISEASE

The recommended oral antibiotics for adults and children with mild leptospirosis include doxycycline (not recommended in children 8 years of age or less) or azithromycin as first-line treatment, with ampicillin or amoxicillin as alternative first-line agents. Azithromycin is non-inferior when compared with doxycycline in the treatment of leptospirosis.^[39] The treatment course is 7 to 10 days (except azithromycin, for which the treatment course is 3 days in adults and is not yet established in children).

Drug	Dose	Duration
Doxycycline	100 mg PO twice a day	7-10 days
Amoxicillin	500 mg PO four times a day	7-10days
Ampicillin	500-750 mg PO four times a day	7-10 days
Azithromycin	500 mg PO once a day	3 days

MODERATE TO SEVERE DISEASE

Moderate to severe leptospirosis in adults and children is treated with intravenous antibiotic therapy. Benzylpenicillin is recommended as the first-line treatment, with ceftriaxone, cefotaxime, or ampicillin as alternative first-line agents.^[36, 37] Ceftriaxone and cefotaxime have shown equivalent clinical efficacy when compared with benzylpenicillin for the management of severe leptospirosis.^[36, 40, 41] Adults with penicillin and/or cephalosporin allergy should be treated with azithromycin (not recommended below the age of 16 years) or doxycycline. Children with such an allergy should be treated with doxycycline.^[37] Doxycycline and other tetracycline antibiotics may cause permanent tooth discolouration or enamel hypoplasia and are not recommended in children 8 years of age or less. However, their use in this patient group may be considered only in case of severe leptospirosis. Erythromycin is a possible alternative and can be given to children below the age of 8 years. Intravenous therapy is recommended for 7 days.

Drug	Dose	Duration
Penicillin	1.5 million units IV qid	7 days
Ceftriaxone	1 gm IV od	7 days
Cefotaxime	1 gm IV qid	7 days

CHEMOPROPHYLAXIS

For individuals who intend to travel to highly endemic area are likely to get exposed to leptospires. The recommended regimen for pre-exposure prophylaxis for non-pregnant, non-lactating adults is: Doxycycline 200 mg once weekly, to begin 1 to 2 days before exposure and continued throughout the period of exposure.^[42]

Antimicrobial agent recommended for Chemoprophylaxis of Leptospirosis		
Indication	Compound	Dosage
Chemoprophylaxis	Doxycycline	200 mg PO once weekly

SUPPORTIVE THERAPY

The type and degree of supportive measures required in patients with leptospirosis are highly variable and are assessed individually according to the organ involvement.

- Severe disease is associated with the immune phase and may manifest with renal failure, hepatic failure and /or pulmonary hemorrhages (Weil's syndrome). Other presentations during this phase include aseptic meningitis and pancreatitis. Death may occur secondary to cardiac arrhythmias, cardiac failure, or adrenal hemorrhage,
- Patients must be monitored for changes consistent with volume depletion and hemorrhage. Physicians should ensure adequate hydration, correct coagulopathy, and correction of electrolyte disturbances.
- Patients with pulmonary involvement, with or without hemorrhage, may require mechanical ventilation. Intravenous methylprednisolone has been used successfully in patients with pulmonary leptospirosis.^[43]
- Patients with acute renal failure may require acute dialysis in severe disease, taking into consideration the symptoms of fluid overload, acidosis, and hyperkalaemia.^[44]
- Cardiac monitoring is recommended to timely identify arrhythmias secondary to cardiac irritability.

PREVENTION

Prevention of leptospirosis may be achieved by avoidance of high-risk exposures, adoption of protective measures, immunization and use of chemoprophylaxis, in varying combinations depending on environmental circumstances and the degree of human activity.

- Controlling infections in livestock and pets can reduce the risk of human disease, but wildlife reservoirs and contaminated environments complicate prevention. Rodent control can be important, particularly in urban areas.
- Other protective measures include avoiding contact with potentially contaminated water (e.g., lakes), and protecting food from contamination. Improvements in sanitation reduce the risk of leptospirosis in urban slums.
- Environmental modifications such as draining wet areas may decrease the incidence of disease, but are not always feasible.

- Personal hygiene and protective clothing are important preventive measures in high risk occupations. Gloves and protective clothing should be used when working with infected animals or tissues, with the addition of face shields or protective eyewear and face masks when the organisms might be aerosolized.
- Rubber boots decrease the risk of leptospirosis when wading in urine-contaminated water.^[45]

CONCLUSION

Leptospirosis has been recognized as an important emerging zoonotic disease because of its epidemic presence and increasing incidence in both developing and developed countries. Leptospirosis is still a major public health problem in tropical countries, with epidemic outbreaks occurring in the rainy season and after floods. Leptospirosis is preventable. Host/reservoir control measures, environmental control programs and animal vaccination, along with a strong surveillance system may significantly reduce, if not eliminate, the disease. The comprehensive and good understanding of the eco-epidemiological and cultural characteristics of a community that faces the problem of leptospirosis is an essential prerequisite for evolving an effective and acceptable control measure.

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